Thimerosal and Vaccines:
A Report by the Institutes of Medicine

Background

The Centers for Disease Control and Prevention (CDC) and the National Institutes of Health (NIH) asked the Institute of Medicine (IOM) to establish an independent expert committee to review hypotheses about existing immunization safety concerns. The first report on MMR vaccine and autism was issued in April 2001. The IOM released its second report on thimerosal and neurodevelopmental outcomes in October 2001.

CDC and NIH welcome the IOM report as a helpful contribution to the complex scientific and policy decision-making which is ongoing in regard to thimerosal. Given these challenges, CDC and NIH are most grateful to the individual scientists on the IOM Committee and IOM staff members for their dedicated and valuable service to the continued integrity of our national immunization system.

Conclusions

The IOM Immunization Safety Review Committee's most important conclusions were 1) that the evidence is inadequate to accept or reject a causal relationship between exposure to thimerosal from vaccines and the neurodevelopmental disorders of autism, attention deficit hyperactivity disorder (ADHD), and speech or language delay, and 2) that although the hypothesis that exposure to thimerosal-containing vaccines could be associated with neurodevelopmental disorders is not established and rests on indirect and incomplete information, primarily from analogies with methyl mercury and levels of maximum mercury exposure from vaccines given in children, the hypothesis is biologically plausible.

Both conclusions are identical with much earlier Public Health Service (PHS) assessments of the evidence. The IOM conclusions are consistent with the goal, first articulated in July 1999 and reaffirmed in July 2000 by PHS agencies, the Advisory Committee on Immunization Practices (ACIP), the American Academy of Pediatrics, and the American Academy of Family Physicians. The goal was to continue using thimerosal-containing vaccines, while at the same time, taking the precautionary measure of removing or greatly reducing thimerosal from vaccines as soon as possible.

Recommendations

The Committee made the specific recommendation that thimerosal-free DTaP, hep B and Hib vaccines be used in the United States for infants, children and pregnant women. This recommendation is also consonant with the 1999 and 2000 goal, particularly with the actions taken to implement the goal. Thus, since 1999, four replacement vaccines without thimerosal or with only greatly reduced trace amounts have been introduced in rapid succession for hepatitis B (September 1999 and March 2000), Hib (July 2000), and DTaP (March 2001). Since April 2001, all seven vaccines that are being made today and recommended for use among all children are now without thimerosal or with only trace amounts (hepatitis B, Hib, DTaP vaccines which

formerly contained thimerosal as a preservative and MMR, Polio, Varicella, and Pneumococcal vaccines which have never contained thimerosal). Furthermore, as of October 2001, the vast majority of the supplies of DTaP, Hib, and hep B vaccines are without thimerosal or with only trace amounts.

The committee also noted that in cases where only vaccines containing the preservative thimerosal are available, the vaccines should be administered rather than foregoing immunization. The committee stated that "While the health effects of thimerosal are uncertain, we know for sure that these vaccines protect against real, proven threats to unvaccinated infants, children, and pregnant women."

Next Steps

The IOM Committee''s specific recommendation that only thimerosal free DTaP, Hib, and hepatitis B vaccines be used, even though there might be a very small number of remaining doses of thimerosal- containing vaccines in the supply chain, will be considered by the ACIP. In the meantime, there are no changes in the ACIP''s current recommendations to use all available DTaP, Hib, and hep B vaccines without regard to thimerosal content. All DTaP, Hib, and hep B vaccines were judged to be safe and effective by experts in 1999 when the goal to remove thimerosal was first set. These vaccines are judged no less safe by experts today, even as they are being phased out.

The Committee has also made helpful recommendations about policy and research topics which are central to fully resolving the outstanding issues related to thimerosal. These also will be considered in depth by the PHS agencies and their advisory bodies over the next few weeks.

The full IOM report can be viewed at
http://www.nap.edu/books/0309076366/html/

Questions and Answers About the IOM Report

Why was the report done?

Issues involving the safety of vaccines, particularly childhood vaccines, continue to concern members of the public, health care professionals, the public health community, the media, Congress, vaccine companies, and federal agencies.

In response to the concerns, the CDC and the National Institutes of Health (NIH) asked the National Academy of Sciences' Institute of Medicine to establish an independent expert committee to review hypotheses about existing and emerging immunization safety concerns. The first of these reviews was an examination of the possible link between the use of the measles, mumps, and rubella (MMR) vaccine and autism. The committee concluded that the evidence favors refection of a causal relationship at the population level between MMR vaccines and autistic spectrum disorders (ASD). The Committee noted that its conclusion does not exclude the possibility that MMR vaccine could contribute to ASD in a small number of children because the epidemiological evidence lacks the precision to assess rare occurrences of a response to MMR vaccine leading to ASD. Additionally, the proposed biological models linking MMR vaccine to ASD, although far from established, are nevertheless

not disproved.

The report on thimerosal-containing vaccines and neurodevelopmental disorders is the second review completed by the IOM's Immunization Safety Review Committee.

The Immunization Safety Review Committee is composed of 15 expert members from pediatrics, neurology, immunology, internal medicine, infectious diseases, genetics, epidemiology, biostatistics, risk perception and communications, decision analysis, public health, nursing, and ethics. To eliminate any real or perceived notion, the committee members were selected on the basis of a strict criteria to eliminate any potential or perceived conflict of interest.

How does the committee examine a hypothesis?

For each hypothesis to be examined, the committee assesses both the scientific plausibility of the issue and its significance in a broader societal context. The scientific plausibility is based on two parts: the biologic plausibility (if it is biologically possible) and causality (an examination of the evidence regarding a possible relation between the vaccine and the adverse event). The significance assessment considers the nature of the health risks associated with the vaccine-preventable disease and with the adverse event in question and other societal concerns. The findings of the plausibility and significance assessments provide the basis for the committee's recommendations.

What were the findings of the IOM's report?

The IOM's Immunization Safety Review Committee concluded that the evidence is inadequate to accept or reject a causal relationship between exposure to thimerosal from vaccines and the neurodevelopmental disorders of autism, attention deficit hyperactivity disorder (ADHD), and speech or language delay. Although the hypothesis that exposure to thimerosal-containing vaccines could be associated with neurodevelopmental disorders is not established and rests on indirect and incomplete information, primarily from analogies with methylmercury and levels of maximum mercury exposure from vaccines given in children, the committee also concluded that the hypothesis is biologically plausible.

The committee believed that the effort to remove thimerosal from vaccines was "a prudent measure in support of the public health goal to reduce mercury exposure of infants and children as much as possible." Furthermore, in this regard, the committee urged that "full consideration be given to removing thimerosal from any biological product to which infants, children, and pregnant women are exposed."

Policy Review and Analysis

The committee recommended the following:

- that thimerosal-free DTaP, hepatitis B, and Hib vaccines be used in the United States, despite the fact that there might be remaining supplies of thimerosal-containing vaccine available
- that full consideration be given by appropriate professional societies and government agencies to removing thimerosal from vaccines administered to infants, children, or pregnant women in the United States

- appropriate professional societies and governmental agencies review their policies about the non-vaccine biological and pharmaceutical products that contain thimerosal and are used by infants, children, and pregnant women in the United States
- that policy analysis be conducted that will inform these discussions in the future
- that a review and assessment be conducted of how public health policy decisions are made under uncertainty
- that a review be conducted of the strategies used to communicate rapid changes in vaccine policy, and that it recommend research on how to improve those strategies

Public Health and Biomedical Research

The committee recommended a diverse public health and biomedical research portfolio. This will be most effective if it involves several different agencies (thus maximizing resources), provides some findings fairly quickly, and utilizes a variety of approaches.

The committee's recommendations included the following:

- case-control studies examining the potential link between neurodevelopmental disorders and thimerosal-containing vaccines
- Further analysis of neurodevelopmental outcomes in these populations
- epidemiological studies that compare the incidence and prevalence of neurodevelopmental disorders before and after the removal of thimerosal from vaccines
- an increased effort to identify the primary sources and levels of prenatal and postnatal exposure to thimerosal (e.g., Rho (D) Immune Globulin, which is given to Rh-negative mothers during pregnancy) and other forms of mercury (e.g., maternal consumption of fish) in infants, children, and pregnant women
- research on how children, including those diagnosed with neurodevelopmental disorders, metabolize and excrete metals—particularly mercury
- continued research on theoretical modeling of ethylmercury exposures, including the incremental burden of thimerosal on background mercury exposure from other sources
- careful, rigorous, and scientific investigations of chelation when used in children with neurodevelopmental disorders, especially autism
- research to identify a safe, effective, and inexpensive alternative to thimerosal for countries that decide they need to switch
- research in appropriate animal models on neurodevelopmental effects of ethylmercury

How much thimerosal-containing DTaP, hepatitis B, and Hib vaccines are available for use in the United States?

As of October 2001, the vast majority of the supplies of DTaP, Hib, and hepatitis B vaccines are without thimerosal or with only trace amounts.

What are the ACIP recommendations regarding DTaP, hepatitis B and Hib vaccines that contain thimerosal?

The use of any DTaP, hepatitis B, and Hib vaccine should continue according to the currently recommended schedule. The risk of not vaccinating children on time to protect them from these diseases is believed to far outweigh the slight risk, if any, of exposure to thimerosal-containing vaccines which are still available.

Has the Advisory Committee on Immunization Practices (ACIP) considered recommending only thimerosal-free vaccines?

The ACIP met in June 2001 to review the progress in achieving the goal of removing thimerosal-containing vaccines from the routinely recommended childhood immunization schedule. At that time, they chose not to make any changes to their previous recommendation, which stated that thimerosal-containing or thimerosal-free vaccines were equally acceptable for use. The ACIP determined that the large risks of not vaccinating children far outweigh the unknown and probably much smaller risk, if any, of cumulative exposure to thimerosal-containing vaccines over the first six months of life. The ACIP will reconsider this issue at its next meeting on October 17-18 in Atlanta, GA.

Since the influenza vaccine contains thimerosal, why do influenza recommendations continue to include pregnant women?

All influenza vaccines contain thimerosal; however, ACIP recommends no changes in the influenza vaccination guidelines, including those for children and pregnant women. Evidence suggests that children with certain medical conditions (e.g., cardiopulmonary disease, including asthma and immunodeficiency conditions) are at substantially increased risk for complications of influenza. During the influenza season rates of hospitalizations for otherwise healthy women in their second or third trimester of pregnancy are similar to those for cardiopulmonary problems from influenza disease among persons aged greater than or equal to 65 years who do not have a chronic medical illness and for whom influenza vaccination also is recommended. Pregnant women with chronic medical conditions are at higher risk and have a hospitalization rate more than two times greater than among pregnant women without other high-risk medical conditions.

A substantial safety margin has been incorporated into the health guidance values for organic mercury exposure developed by the Agency for Toxic Substances and Disease Registry and other agencies. ACIP concluded that the benefits of influenza vaccine outweigh the potential risks for thimerosal.

The IOM recommended the use of thimerosal-free DTaP, hepatitis B, and Hib vaccines in the United States despite the fact that there might be remaining

supplies of thimerosal-containing vaccines available. Why doesn't the FDA recall all thimerosal-containing vaccines intended for use in infants and small children?

A recall of thimerosal-containing vaccines is not warranted because currently available data show that these products are safe and effective. Federal law is specific about the criteria that must be met before FDA can enforce a mandatory recall of a regulated product. Under section 351(d) of the Public Health Service Act, a licensed vaccine (or other biological product) shall be recalled if FDA determines that it "presents an imminent or substantial hazard to the public health..." FDA does not believe that thimerosal-containing vaccines present an imminent or substantial hazard to the public health because available scientific data do not establish that exposure to thimerosal in vaccines can cause neurodevelopmental disorders. Additional studies on the potential for adverse effects of mercury in vaccines are continuing. Results of these studies will be closely monitored.

FDA regulations also provide for a voluntary recall of products regulated by the FDA (21 CFR, Part 7). A firm may withdraw a product from the market, of its own volition, at any time. In addition, FDA may request a firm to recall a product that is in violation of FDA laws and regulations and that presents a risk of injury or gross deception, or is otherwise defective; an agency request for recall is reserved for urgent situations such as those that are necessary to protect the public health. FDA has concluded that voluntary recall is not warranted because vaccines that contain thimerosal as a preservative are not violative products and there are no conclusive data that they present a risk of injury.

However, the department concurs with the IOM that it is prudent to avoid mercury exposure from vaccines, indeed, from all sources. Accordingly, the department's Inter-Agency Vaccine Group has worked with manufacturers to remove or reduce thimerosal from vaccines. The FDA expedited reviews of manufacturers' supplements to their product license applications to eliminate or reduce the mercury content in vaccines to help assure that the Public Health Service goal of replacement of thimerosal-containing vaccines takes place as expeditiously as possible.

Thus, since March 2001, all routinely administered pediatric vaccines are now being manufactured either in thimerosal-free or thimerosal-reduced (greater than 95 percent reduction) presentations, and infant exposure to mercury from vaccines is unlikely to exceed any federal guidelines.

What are the next steps related to the IOM report?

The review of the concerns that has been carried out by the independent expert panel assembled by the IOM will contribute to maintaining public confidence in our national immunization program and assuring the continued protection of U.S. children against vaccine-preventable diseases in an effective and safe manner. The recommendations made by this expert panel are under review by the department''s Inter-Agency Vaccine Group. The ACIP will consider the IOM''s recommendations at its next meeting, in Atlanta, GA, on October 17-18, 2001. In the meantime, ACIP childhood immunization recommendations remain unchanged.